Remarks

Claims 34-60 are pending in the subject application. Applicants acknowledge that claims 41, 42 and 46-60 have been withdrawn from further consideration as being drawn to a non-elected invention. As indicated by the Examiner in the Restriction Requirement dated July 12, 2007, only claims 1-26 were pending due to an Article 34 amendment when the subject application entered the national phase. Accordingly, when the Preliminary Amendment dated April 18, 2005 was filed, claims 1-26 should have been canceled rather than the original claims 1-33 as filed in the corresponding PCT application. By this Amendment, Applicants have canceled claims 1-53 and added new claims 54-72 to address the claim numbering issue. Support for the new claims can be found throughout the subject specification (see, for example, page 13, lines 7-16 and Example 5) and in the claims as originally filed. Entry and consideration of the new claims presented herein is respectfully requested. Accordingly, claims 54-72 are currently before the Examiner (with claims 57, 58 and 61-64, 66, 67 and 69-72 standing withdrawn from consideration as being directed to a non-elected invention). Claims 54, 55, 56, 59, 60, 65 and 68 read on the elected species. Favorable consideration of the pending claims is respectfully requested.

At the outset, Applicants note that the Office Action suggests revising the as-filed specification to conform with the Patent Office's preferred layout for a specification. Applicants respectfully submit that there is no statutory or rule-based authority for requiring submission of a specification in the format indicated to be the "preferred layout" by the Patent Office in the M.P.E.P. at section 601(I) and elect to retain the specification in its present form at this time; however, Applicants may submit a revised specification, including the heading suggested in the Office Action, at a later time.

Figure 5 is objected to because it lacks labels for Panels A and B described on page 33 of the specification. By this Amendment, Figure 5 has been amended to clearly indicate Figure 5A and Figure 5B. No new matter has been added by these amendments. Entry and consideration of the replacement figure is respectfully requested. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

The subject specification has been objected to on the grounds that it does not comply with 37 CFR §1.821 through 1.825. Specifically, the Office Action indicates that the specification at Table

2, pages 43 and 44, and Figure 6, panel b disclose nucleotide sequences in excess of 9 bases that are not accompanied by a sequence identifier number. Applicants respectfully assert that an Amendment in Response to a Notice Under 37 CFR §§1.821-1.825 was filed on March 13, 2006 which replaced Table 2 to provide sequence identifier numbers for the sequences listed therein and which amended the description of Figure 6 in the specification to include the sequence identifier numbers identified in Figure 6B. Applicants point out that claim 44 was also amended. The replacement sequence listing was filed on February 16, 2006. By this Amendment, Applicants have amended Table 2 to remove the "boxes" in the description of SEQ ID NOs: 24-29. Support for the amendment can be found, for example, on pages 43-44 of the as-filed specification. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claim 38 is objected to because of informalities. Applicants appreciate the Examiner's careful review of the claims. Claim 38 (now new claim 56) has been amended to attend to the formality issues thereby rendering this objection moot. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 35 and 44 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully assert that the claims as filed are definite. Claim 35 is indefinite because it is unclear what are the metes and bounds of "unwanted" PRF1 activity. Applicants respectfully submit that this issue is now moot in view of the cancellation of claim 35. Additionally, claim 44 (now new claim 60) is indefinite because it requires an siRNA molecule comprising a sequence of 50 nucleotides, but siRNAs are recognized in the art to be generally of 21-23 nucleotides in length. Applicants have amended the claim to indicate that the recited nucleic acid sequence is a portion of a construct that encodes an siRNA. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 34-40 and 43-45 (now new claims 54-56 and 59-61) are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. The Office Action indicates that the subject specification is enabled for a method of inhibiting the growth of a tumor or a precancerous growth, wherein the tumor or precancerous growth is characterized by dysregulation of phosphoinositide 3-kinase (PI3K) signaling, by delivering directly to the tumor or precancerous growth an siRNA that causes degradation of an mRNA encoding PRF1, but is not enabled for

methods of inhibiting the growth of a tumor or a precancerous growth by systemic delivery of siRNA. Applicants respectfully assert that the claims as filed are enabled; however, in an effort to advance prosecution in this matter at this time, Applicants have amended the claims and respectfully submit that this issue is now moot.

The Office Action also argues that RNA interference was recognized as not enabled for therapeutic purposes with respect to the systemic administration of RNAi molecules to a subject in need of treatment. Additionally, the Office Action argues that given the recognized unpredictability in the art of nucleic acid therapeutics, one of skill would still require specific guidance to practice the claimed methods *in vivo* in any organism or any mammal, with the resultant specified biological effect. However, the specification does not provide either examples or the required guidance to allow one of skill in the art to reliably and predictably obtain success using the claimed methods *in vivo.* The specification does not overcome the art recognized obstacles to *in vivo* RNAi, particularly in terms of specific targeting and delivery of the dsRNA to a whole organism. As a result one of skill in the art would have to perform undue experimentation in order to practice the claimed invention. Based on the instant disclosure, one of skill in the art would not know, *a priori,* if practicing of the instant method comprising introducing a siRNA of the invention, *in vivo,* to a whole organism, would result in the successful inhibition of the target gene in any particular cell, tissue or organ of said organism. Thus, one of skill in the art could not practice the invention commensurate in scope with the claims. The Office Action also cites to a number of references in its reasoning that the claimed invention is not enabled for the systemic administration for RNAi molecules to a subject. The Office Action also appears to argue that due to a lack of disclosed formulations and techniques allegedly not known in the art, that the specification does not provide adequate guidance as to how one skilled in the art should administer RNAi molecules to effect a therapeutic benefit. Applicants traverse.

Applicants respectfully submit that the degree of guidance argued to be necessary in the Office Action is not required to meet the enablement requirement of 35 U.S.C. § 112. *See In re Chilowsky*, 229 F.2d 457, 460, 108 U.S.P.Q. 321, 324 (C.C.P.A. 1956) ("[T]he applicant 'may begin at the point where his invention begins, and describe what he has made that is new and what it replaces of the old. That which is common and well known is as if it were written out in the patent

and delincated in the drawings."'); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1987) ("[A] patent need not teach, and preferably omits, what is well known in the art."); *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) ("That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue."') (emphasis in original).

While the Office Action cites to a number of references in support of the position articulated in the Office Action of January 23, 2008, Applicants respectfully submit that these articles and articulated grounds of rejection fail to establish that the claimed invention is not enabled. For example, the Office Action appears to overlook Table 1 of Opalinska *et al.* where a number of clinical trials and their outcomes are presented (page 508) and planned clinical trials are discussed (page 511). As would be noted from those reported clinical trials, nucleic acid based therapeutic agents have been administered to individuals intravenously and disease remission or stabilization was observed in the treated individuals. This information, available and known to those skilled in the art at the time the subject patent application was filed, would not appear to support the contention that those skilled in the art would not know the appropriate means and vehicles for the administration of nucleic acid based therapeutic agents to an individual.

The Office Action also cites several post-filing references that review problems that have been encountered in trying to move nucleic acid-based therapies from the laboratory to the clinic. Applicants respectfully submit that these references are not relevant to the patentability of the claimed invention. As the Patent Office is aware, clinical efficacy is not required to enable the claims on appeal. *See CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003) ("Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace."). Applicants also respectfully submit that the Office Action appears to require the as-filed specification provide teachings demonstrating the clinical effectiveness of the claimed invention. As also noted by the Patent Office's reviewing court, it is improper to confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995). Particularly, the *Brana* court held that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of

further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *Id.* at 1568. (The court's reference to "usefulness" was in the context of the how-to-use prong of 35 U.S.C. § 112, first paragraph; the rejection on appeal was for nonenablement. *See id.* at 1564.). Accordingly, Applicants respectfully submit that the claimed invention is enabled for inhibiting the growth of a tumor or a precancerous growth by both systemic and site specific administration and reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 34-37 and 39 (now new claims 54 and 55) are rejected under 35 U.S.C. § 102(b) as anticipated by Hu *et al.* (2000). The Office Action states that Hu *et al.* teach a method of inhibiting growth of ovarian cancer cells in a mouse by administration of LY294002, which is an inhibitor of PI3K. In addition, claims 34-37, 39 and 45 (now new claims 54, 55 and 61) are rejected under 35 U.S.C. § 102(b) as anticipated by Allen *et al.* (2002). The Office Action indicates that Allen *et al.* teach a method in which CI-1033, an inhibitor of PI3K, was used to treat breast cancer. Finally, claims 34-37, 39 and 45 (now new claims 54, 55 and 61) are rejected under 35 U.S.C. § 102(b) as anticipated by Goldenberg (1999) as evidenced by Yakes *et al.* (2002). The Office Action cites Goldenberg as teaching a method of treating breast cancer in humans by administration of Trastuzumab (Herceptin). Yakes provides evidence that Trastuzumab inhibits PI3K signaling and Akt activity. Applicants respectfully assert that the references do not anticipate the claimed invention as each of the references fails to teach a composition comprising a nucleic acid that inhibits the activity of PRF1, said nucleic acid being selected from an aptamer, an aptazyme, a ribozyme, a spiegelmer, an antisense oligonucleotide and or siRNA. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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FCE/sl
Attachment: Replacement Figure 5